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Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women

The Premenopausal Breast Cancer Collaborative Group

 Supplemental content

IMPORTANCE The association between increasing body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and risk of breast cancer is unique in cancer epidemiology in that a crossover effect exists, with risk reduction before and risk increase after menopause. The inverse association with premenopausal breast cancer risk is poorly characterized but might be important in the understanding of breast cancer causation.

OBJECTIVE To investigate the association of BMI with premenopausal breast cancer risk, in particular by age at BMI, attained age, risk factors for breast cancer, and tumor characteristics.

DESIGN, SETTING, AND PARTICIPANTS This multicenter analysis used pooled individual-level data from 758 592 premenopausal women from 19 prospective cohorts to estimate hazard ratios (HRs) of premenopausal breast cancer in association with BMI from ages 18 through 54 years using Cox proportional hazards regression analysis. Median follow-up was 9.3 years (interquartile range, 4.9-13.5 years) per participant, with 13 082 incident cases of breast cancer. Participants were recruited from January 1, 1963, through December 31, 2013, and data were analyzed from September 1, 2013, through December 31, 2017.

EXPOSURES Body mass index at ages 18 to 24, 25 to 34, 35 to 44, and 45 to 54 years.

MAIN OUTCOMES AND MEASURES Invasive or in situ premenopausal breast cancer.

RESULTS Among the 758 592 premenopausal women (median age, 40.6 years; interquartile range, 35.2-45.5 years) included in the analysis, inverse linear associations of BMI with breast cancer risk were found that were stronger for BMI at ages 18 to 24 years (HR per 5 kg/m² [5.0-U] difference, 0.77; 95% CI, 0.73-0.80) than for BMI at ages 45 to 54 years (HR per 5.0-U difference, 0.88; 95% CI, 0.86-0.91). The inverse associations were observed even among nonoverweight women. There was a 4.2-fold risk gradient between the highest and lowest BMI categories (BMI ≥ 35.0 vs < 17.0) at ages 18 to 24 years (HR, 0.24; 95% CI, 0.14-0.40). Hazard ratios did not appreciably vary by attained age or between strata of other breast cancer risk factors. Associations were stronger for estrogen receptor-positive and/or progesterone receptor-positive than for hormone receptor-negative breast cancer for BMI at every age group (eg, for BMI at age 18 to 24 years: HR per 5.0-U difference for estrogen receptor-positive and progesterone receptor-positive tumors, 0.76 [95% CI, 0.70-0.81] vs hormone receptor-negative tumors, 0.85 [95% CI, 0.76-0.95]); BMI at ages 25 to 54 years was not consistently associated with triple-negative or hormone receptor-negative breast cancer overall.

CONCLUSIONS AND RELEVANCE The results of this study suggest that increased adiposity is associated with a reduced risk of premenopausal breast cancer at a greater magnitude than previously shown and across the entire distribution of BMI. The strongest associations of risk were observed for BMI in early adulthood. Understanding the biological mechanisms underlying these associations could have important preventive potential.

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Breast cancer is the most commonly diagnosed cancer among women worldwide, accounting for 25% of female cancer cases at all ages and a greater percentage among young women.¹ Its complex etiology involves an unusually large range of factors, of which adiposity, often assessed as body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), is important and appears to have opposing effects at premenopausal and postmenopausal ages.

Increased adiposity in childhood and before menopause has been reported to be inversely associated with the risk of breast cancer diagnosed at premenopausal and postmenopausal ages, whereas increased adiposity after menopause is positively associated with risk.²⁻¹¹ However, because incidence rates are lower among premenopausal than postmenopausal women, individual studies have had limited ability to investigate the association of BMI with the risk of premenopausal breast cancer. Past studies have been case-control studies, with potential for bias, and most prospective studies have had modest numbers of cases, except for some recent studies in Asian^{12,13} or Jewish Israeli¹⁴ populations, but have not assessed risk at different ages, by tumor type, and by menopausal status at breast cancer diagnosis. Meta-analyses have aggregated studies that differed in age at BMI assessment, attained age of participants, and degree of adjustment for potential confounding, and results were not stratified by other risk factors.^{2-5,15-18} Some studies suggest that the association of premenopausal adiposity with risk varies by tumor characteristics,^{2,7,17-19} but larger studies are needed to provide stable estimates by hormone receptor status or intrinsic tumor subtype.

To undertake a more powerful and systematic analysis of the association of BMI with breast cancer risk in premenopausal women, we pooled individual-level data from 758 592 women, including 13 082 cases of breast cancer, from 19 prospective cohort studies using data from recruitment and follow-up questionnaires. We aimed to estimate the relative risk associated with BMI at different ages, age at breast cancer diagnosis, and breast cancer characteristics and to explore whether associations were modified by other risk factors for breast cancer.

Methods

Information on the Premenopausal Breast Cancer Collaborative Group, a collaboration facilitated by the National Cancer Institute Cohort Consortium, has been published previously.²⁰ In short, individual-level data were pooled from 19 prospective cohorts in North America (n = 9), Europe (n = 7), Asia (n = 2), and Australia (n = 1),²⁰ with participants recruited from January 1, 1963, through December 31, 2013 and at least 100 breast cancer cases diagnosed before 55 years of age. Data were harmonized to a common template for 1 to 16 questionnaire rounds per study. Full details of the study cohorts are given in the eMethods in the Supplement. All contributing studies gained approval from institutional review boards and obtained consent from participants as per country-specific requirements.

Key Points

Question What is the association between body mass index and risk for breast cancer diagnosed before menopause?

Finding In this large pooled analysis of data on 758 592 premenopausal women, an inverse association of breast cancer risk with body mass index at 18 through 54 years of age was found, most strongly for body mass index at ages 18 through 24 years. The inverse association was strongest for hormone receptor-positive breast cancer, was evident across the entire distribution of body mass index, and did not materially vary by attained age or other characteristics of women.

Meaning Increased adiposity, in particular during early adulthood, may be associated with reductions in the risk of premenopausal breast cancer.

We used information on self-reported or measured current weight and height from multiple questionnaire rounds and information reported on questionnaires about weight at ages before study entry to construct BMI within the age ranges of 18 to 24, 25 to 34, 35 to 44, and 45 to 54 years. We categorized BMI according to World Health Organization definitions.²¹ The analysis included all participants who were premenopausal, had no personal history of breast cancer at study entry, and had data for premenopausal BMI available.

All breast cancers included in this analysis occurred before menopause, with the main analytic end point being invasive or in situ premenopausal breast cancer overall. However, we also analyzed separately by invasive and in situ cancer, by immunohistochemistry data on estrogen receptor (ER) and progesterone receptor (PR) status, and by clinicopathologic surrogate definitions of intrinsic breast cancer subtype.

Hazard ratios (HRs) were obtained as estimates of the relative risk of breast cancer from Cox proportional hazards regression models²² with attained age as the underlying timescale. Follow-up for breast cancer started at study entry or the age after enrollment to which the BMI applied. Follow-up ended at breast cancer diagnosis, menopause (or hysterectomy), last follow-up, death, or age 55 years, whichever occurred first.

We first generated cohort-specific relative risk estimates and obtained a pooled estimate with a 2-stage model.²³ Because no appreciable between-study heterogeneity was detected using the I^2 statistic,²⁴ the data were analyzed in a pooled data set. All presented analyses were adjusted for attained age (implicit in the Cox proportional hazards regression model), cohort, year of birth, age at menarche, age at first birth, time since last birth, parity, and family history of breast cancer. Covariate information was time updated, when possible, with information from follow-up questionnaires.

We analyzed BMI separately as categorical and continuous variables (per 5 kg/m² [5.0-U] difference), assuming a log-linear dose-response association, the validity of which was checked using restricted cubic spline models.²⁵ We tested for effect modification by other risk factors for breast cancer and by attained age using log-likelihood ratio tests.²⁶ Analyses by breast tumor subtype were conducted using an augmentation method.²⁷ This method allows estimation of separate risk

factor associations for type-specific outcomes in a single model stratified on outcome type, obtained from a data set in which separate observations on each participant have been created for each outcome. Conducted sensitivity analyses are outlined in the eMethods in the [Supplement](#). We used Stata, version 14.2 (StataCorp) for all analyses, with $P < .05$ indicating significance.²⁸

Results

The analyses included 758 592 women (median age, 40.6 years; interquartile range, 35.2-45.5 years), among whom 13 082 in situ or invasive breast cancer cases occurred during 7.2 million premenopausal years of follow-up (median, 9.3 years; interquartile range, 4.9-13.5 years) (eTable 1 in the [Supplement](#)). Weight was provided at 1 to 14 (median, 2) follow-up rounds per study and was self-reported for 88.9% to 99.6% of weights, depending on age. Weight at ages 18 to 24 years was retrospectively reported for 96.9% and at later ages for less than 10% of women. Obesity (BMI ≥ 30.0) was more common in women who were 45 years or older (11.1%), were nulliparous (12.4%), had an early menarche (17.0%), had a family history of breast cancer (12.8%), or were black (26.8%) (Table).

Increasing BMI was linearly associated with decreasing risk of breast cancer in the restricted cubic spline models (eFigures 1 and 2 in the [Supplement](#)), except that, for some ages and tumor types, there appeared to be a leveling of risk for underweight women (BMI < 18.5) compared with those in the normal weight range (BMI, 18.5-24.9). We therefore restricted the linear modeling of BMI to values of 18.5 or greater.

Hazard ratios for breast cancer decreased with increasing BMI category (Figure 1), more for BMI at younger than older ages, with a risk reduction of 23% per 5.0-U difference (HR, 0.77; 95% CI, 0.73-0.80) for BMI at ages 18 to 24 years and 12% (HR, 0.88; 95% CI, 0.86-0.91) for BMI at 45 to 54 years. The risk gradient was 4.2-fold between the highest and lowest BMI categories (BMI ≥ 35.0 vs < 17.0) at ages 18 to 24 years (HR, 0.24; 95% CI, 0.14-0.40). Significant differences in relative risk were present even within the normal range of BMI (for 23.0-24.9 vs 18.5-22.9: HR, 0.80; 95% CI, 0.75-0.86). The HRs for BMI at ages 18 to 24 years remained statistically significant after additional adjustment for most recent BMI (HR per 5.0-U increase, 0.80; 95% CI, 0.76-0.84). We found no appreciable heterogeneity in the association between studies (eFigure 3A-D in the [Supplement](#)).

Weight at ages 18 to 24 years was correlated with weights at older ages ($r = 0.70$ for ages 25-34, $r = 0.63$ for ages 35-44, and $r = 0.55$ for ages 45-54 years). When we adjusted the analyses of breast cancer risk in Figure 2 for BMI at ages 18 to 24 years, the HRs per 5.0-U increase were 0.92 (95% CI, 0.88-0.97) for BMI at ages 25 to 34 years, 0.93 (95% CI, 0.91-0.96) at ages 35 to 44 years, and 0.91 (95% CI, 0.88-0.95) at ages 45 to 54 years (Figure 2 and eTable 2 in the [Supplement](#)). The magnitude of the inverse associations was similar between categories of attained age to age 55 years (eFigure 4 in the [Supplement](#)).

Incident cases of breast cancer included 10 836 invasive and 2138 in situ breast cancers. Associations with risk per

5.0-U difference in BMI were significantly larger for in situ (HR, 0.76; 95% CI, 0.69-0.85) than for invasive breast cancer (HR, 0.88; 95% CI, 0.84-0.92) ($P = .02$ for interaction) for BMI at ages 25 to 34 years; difference in associations were also found for in situ (HR, 0.81; 95% CI, 0.76-0.86) and invasive breast cancer (HR, 0.88; 95% CI, 0.86-0.90; $P = .01$ for interaction) at 35 to 44 years (eTable 3 in the [Supplement](#)). The percentage of all breast cancers that were in situ did not appreciably vary by BMI, and women with higher BMI were more likely to have had a screening mammogram (eTable 4 in the [Supplement](#)).

The ER and/or PR status was known for 7812 cases, 7002 (89.6%) of which were invasive. We did not observe consistent significant differences in HRs for ER-positive vs ER-negative or PR-positive vs PR-negative breast cancer (eTable 5 in the [Supplement](#)). When considering ER and PR jointly, ER-positive and/or PR-positive breast cancer showed stronger associations with BMI at ages 18 to 24 years (eg, for ER-positive and PR-positive, HR, 0.75; 95% CI, 0.70-0.81) than did hormone receptor-negative breast cancer; however, the association was still significant for ER-negative and PR-negative breast cancer (HR, 0.85; 95% CI, 0.76-0.95) (eFigure 5 in the [Supplement](#)). Body mass index at older ages was not associated with hormone receptor-negative breast cancer risk. In analyses by intrinsic breast cancer subtype (Figure 3), the non-luminal (ER-negative and PR-negative) subtype was inversely associated with BMI at ages 18 to 24 (HR, 0.86; 95% CI, 0.77-0.96) and 45 to 54 years (HR, 0.90; 95% CI, 0.84-0.98), but not with BMI at ages 25 to 34 and 35 to 44 years. No association of BMI at 25 years or older with triple-negative breast cancer or of BMI at 35 years or older with *ERBB2/HER2*-enriched breast cancer was found.

Hazard ratios per 5.0-U difference in BMI were not significantly different between strata of most risk factors for breast cancer, including race/ethnicity (for BMI at ages 18 to 24 years: HR for black women, 0.84 [95% CI, 0.76-0.93]; HR for Asian women, 0.69 [95% CI, 0.40-1.18]; and HR for white women, 0.73 [95% CI, 0.70-0.77]; $P = .08$ for interaction) (eFigure 6 and eTable 6 in the [Supplement](#)). Hazard ratios were greater for never users compared with than ever users of oral contraceptives (at baseline for most studies) for BMI at ages 18 to 24 years (HR, 0.68 [95% CI, 0.61-0.76] vs 0.79 [95% CI, 0.75-0.83]; $P = .02$ for interaction) and ages 35 to 44 (HR, 0.81 [95% CI, 0.77-0.86] vs 0.88 [95% CI, 0.86-0.91]; $P = .009$ for interaction). The HR was also greater for nulliparous than parous women (HR, 0.79 [95% CI, 0.73-0.87] vs 0.88 [95% CI, 0.84-0.93]; $P = .03$ for interaction) for BMI at ages 25 to 34 years. Results were not materially affected in the sensitivity analyses (eTables 7-9 in the [Supplement](#)) except for those shown in Figure 1.

Discussion

In this large prospective analysis investigating the association between adiposity and breast cancer risk in premenopausal women, we analyzed relative risk by BMI in a larger number of categories than possible in previous studies, re-

Table. Characteristics at Study Recruitment of Women Included in the Analyses

Characteristic	Participants, No. (BMI ≥ 30.0, %)	Person-years of Follow-up, No. (%) ^a	Cancer Cases, No.
BMI ^b			
15.0-16.9	2843	29 293 (0.4)	53
17.0-18.4	20 245	221 540 (3.1)	442
18.5-24.9	499 146	4 901 964 (68.1)	9356
25.0-29.9	159 660	1 375 769 (19.1)	2257
30.0-34.9	51 413	442 769 (6.2)	678
35.0-49.9	25 285	227 485 (3.2)	296
Age at entry, y			
<25	17 627 (9.2)	211 220 (2.9)	74
25-34	167 744 (8.9)	2 585 847 (35.9)	3657
35-44	366 893 (10.1)	3 688 360 (51.2)	7404
≥45	206 328 (11.1)	713 394 (9.9)	1947
Age at menarche, y			
7-11	141 899 (17.0)	1 410 957 (19.6)	2712
12-13	391 822 (9.7)	3 849 467 (53.5)	7117
≥14	195 180 (6.2)	1 715 887 (23.8)	2871
Missing or no periods	29 691 (9.1)	222 509 (3.1)	382
Age at first birth, y			
<25	290 668 (11.2)	2 630 694 (36.5)	4186
25-34	273 023 (8.7)	2 583 161 (35.9)	5364
≥35	19 152 (9.5)	134 836 (1.9)	393
Nulliparous	121 920 (12.4)	1 311 508 (18.2)	2367
Age or whether parous unknown	53 829 (6.7)	538 621 (7.5)	772
No. of births ^c			
1	128 760 (10.4)	1 358 259 (25.2)	2583
2	252 325 (9.4)	2 213 928 (41.0)	4356
3	188 633 (10.8)	1 650 219 (30.6)	2900
Not known	18 341 (6.5)	178 049 (3.3)	172
Family history of breast cancer			
No	556 203 (10.1)	5 576 245 (77.5)	9478
Yes	75 299 (12.8)	625 576 (8.7)	2265
Not known	127 090 (8.4)	997 000 (13.8)	1339
Race/ethnicity			
White	419 130 (10.0)	4 437 300 (61.6)	8437
Black	52 903 (26.8)	586 734 (8.2)	1006
Asian	26 214 (2.5)	212 411 (3.0)	235
Other	7894 (13.7)	89 276 (1.2)	167
Not known	252 451 (7.5)	1 873 100 (26.0)	3237
Birth cohort			
Before 1930	23 849 (9.1)	98 669 (1.4)	178
1930-1939	66 110 (7.7)	655 904 (9.1)	1306
1940-1949	243 663 (8.4)	1 878 359 (26.1)	4088
1950-1959	282 307 (10.9)	2 983 715 (41.4)	5305
1960-1969	101 002 (13.7)	1 183 177 (16.4)	1970
1970-1979	33 904 (11.2)	341 589 (4.7)	219
1980 or later	7757 (8.1)	57 407 (0.8)	16
All	758 592 (10.1)	7 198 821 (100.0)	13 082

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

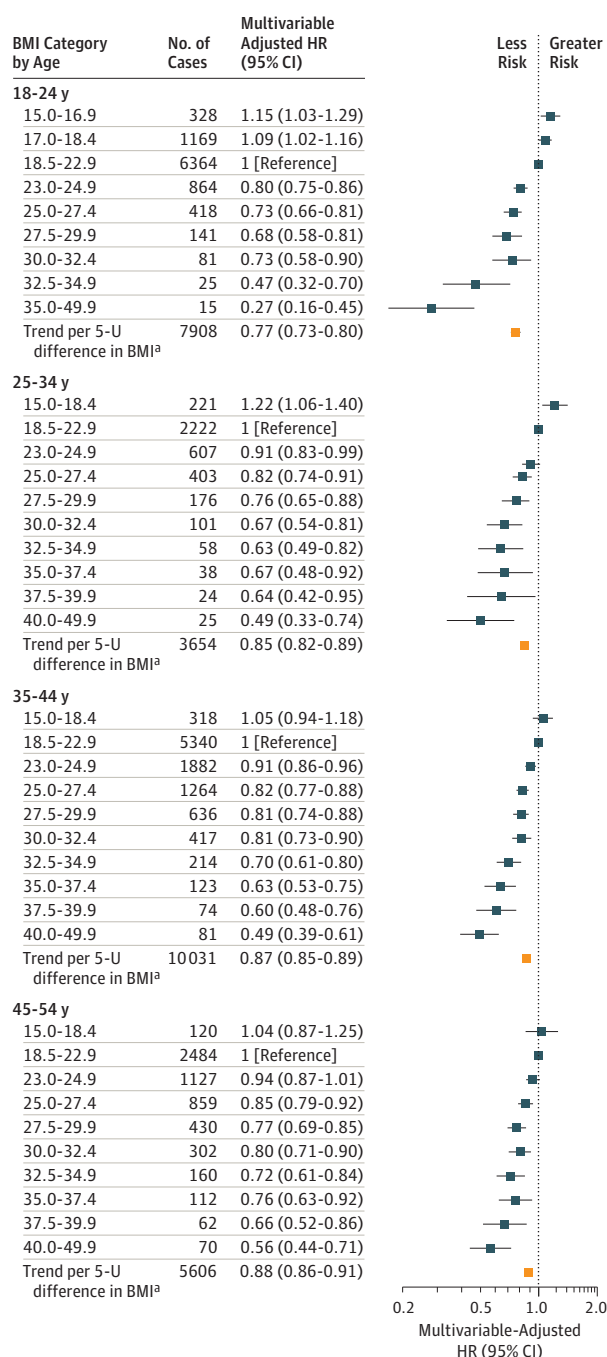
^a Percentages have been rounded and may not total 100. Owing to rounding, person-years may not sum to the total.

^b Indicates at study entry or, if missing, most recent retrospectively reported weight.

^c Includes parous only.

revealing a 4.2-fold risk gradient between women who were underweight vs obese at ages 18 to 24 years and a 1.9- to 2.5-fold risk gradient between these BMI categories at later ages. We

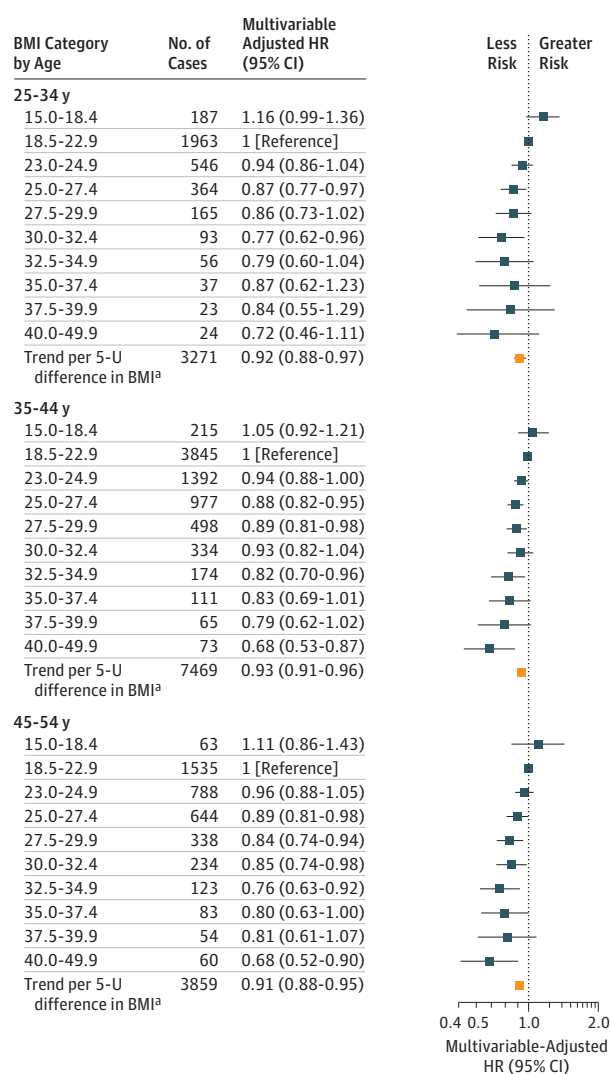
demonstrated that the inverse associations apply to the entire distribution of BMI, with risk variations evident even among women in the nonoverweight range of BMI.

Figure 1. Relative Risk of Premenopausal Breast Cancer Associated With BMI Category, by Age at BMI

Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared. Hazard ratios (HRs) were adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth, and family history of breast cancer.

^a Represents linear trend per 5 kg/m² (5.0-U) difference in BMI from 18.5 to 49.9.

The observed inverse associations are unlikely to be attributable to bias, given that they were present in multiple studies and across strata of birth cohort and risk factors for

Figure 2. Relative Risk of Premenopausal Breast Cancer Associated With BMI and Adjusted for BMI at Ages 18 to 24 Years, by Age at BMI

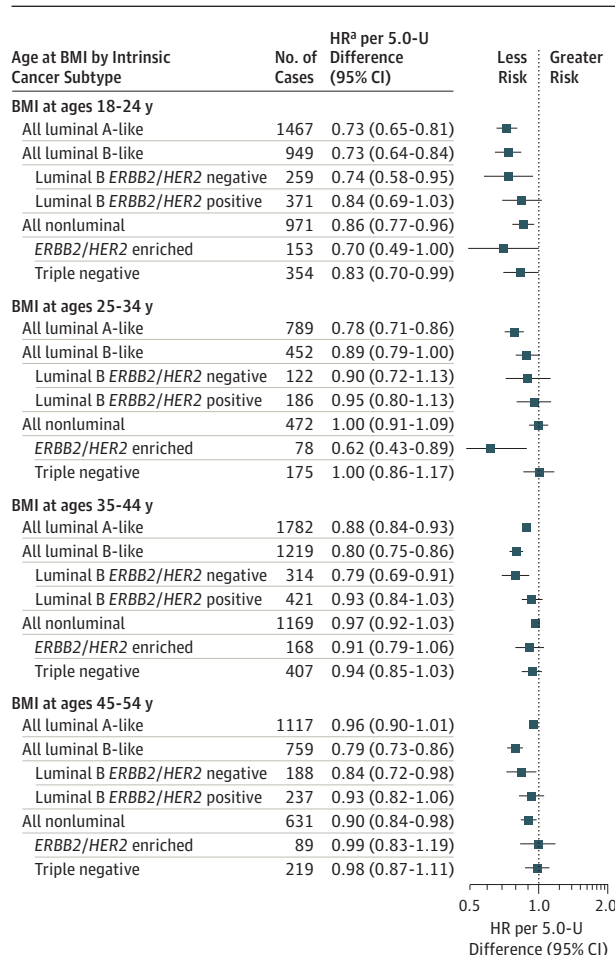
Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared. Hazard ratios (HRs) were adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth, and family history of breast cancer as well as BMI at ages 18 to 24 years.

^a Represents linear trend per 5 kg/m² (5.0-U) difference in BMI from 18.5 to 49.9.

breast cancer. Too few women died during follow-up (3.3% of women with a BMI ≥ 35.0 vs 1.7% with BMI of 18.5-24.9) to explain the inverse associations for death as a competing risk. Our results are also supported as causal rather than artifactual by a mendelian randomization study²⁹ reporting genetically predicted BMI to be inversely associated with breast cancer risk.

The stronger inverse associations of risk with BMI at younger than older ages suggest that adiposity in young adulthood or earlier, if adiposity at approximately 20 years of age is a proxy marker for adiposity in childhood, is the critical factor. No cohorts in our collaboration had information on BMI

Figure 3. Relative Risk of Premenopausal Breast Cancer per 5 kg/m² (5.0-U) Difference in BMI by Age at BMI and Breast Cancer Intrinsic Tumor Subtype



Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared. The luminal A-like subtype includes estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, and *ERBB2/HER2*-negative tumors; luminal B-subtype, all ER-positive and/or PR-positive tumors that are not luminal A-like (subtypes luminal B-like *ERBB2/HER2*-negative and luminal B-like *ERBB2/HER2*-positive); and nonluminal subtype, all ER-negative and PR-negative tumors, regardless of *ERBB2/HER2* status (subtypes *ERBB2/HER2* enriched: ER-negative, PR-negative, and *ERBB2/HER2*-positive; triple-negative: ER-negative, PR-negative, and *ERBB2/HER2*-negative).

^a Represents linear trend per 5.0-U of difference in BMI from 18.5 to 49.9 and are adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth, and family history of breast cancer. Estimates were obtained from 2 augmentation models.²⁷ The first model included luminal A-like, luminal B-like, and nonluminal breast cancer as end points with tests for heterogeneity in effect by tumor type (for BMI at ages 18-24 years, $P = .07$; at ages 25-34 years, $P = .002$; at ages 35-44 years, $P < .001$; at ages 45-54, $P < .001$). Estimates for subtypes of luminal B-like and nonluminal breast cancer were obtained from a second model fitting luminal A-like, luminal B-like *ERBB2/HER2*-positive, luminal B-like *ERBB2/HER2*-negative, *ERBB2/HER2*-enriched, and triple-negative breast cancer as end points.

at younger than 18 years, but published analyses of subjective body size compared with peers at these ages⁷⁻⁹ have found strong inverse associations with premenopausal and postmenopausal breast cancer risk.

Our estimated 12% to 23% reduction in premenopausal breast cancer risk per 5.0-U difference in BMI depending on age is substantially stronger than that from meta-analyses,^{3-5,15,16} which have reported 5% to 9% reductions among women overall without analysis by age at BMI, and a study reporting a 10% reduction using measured BMI at ages 16 to 19 years.¹⁴ We observed that associations of BMI and breast cancer risk did not depend on attained age. We found no previous analyses by premenopausal attained age, but risk reductions with increased early-life BMI have been reported to continue after menopause.^{7,8} The associations of BMI with risk also did not appear to be appreciably modified by risk factors for breast cancer later in life, with the possible exception of nulliparity and oral contraceptive use.

The stronger associations of BMI at ages 25 to 44 years for in situ than for invasive breast cancer might reflect type-specific etiology or the association for in situ cancer being in part attributable to an association of body size with breast screening attendance. However, we found no evidence for this association, given that percentages of in situ cancer were similar across BMI groups.

No previous analyses of hormone receptor status-specific breast cancer by BMI assessed at different premenopausal ages have been performed, to our knowledge. We found that hormone receptor-positive breast cancer was associated with BMI at all ages and that hormone receptor-negative breast cancer overall was associated with BMI at ages 18 to 24 years, but not consistently associated with BMI at later ages; meta-analyses of ER- and PR-negative tumors^{15,17} have found no association, based on age at recruitment. The absence of an association of triple-negative breast cancer with BMI at 25 years or older in our analysis is contrary to previous reports^{18,19} indicating an increased risk of this tumor type with obesity; however, these reports were based on case-control studies¹⁸ and a pooled analysis of women younger than 50 years based on studies of mixed design¹⁹ and therefore are subject to potential biases that are of less concern in prospective cohorts. We observed that *ERBB2/HER2*-enriched breast cancer was associated with BMI at 35 years or younger but not at later ages; the Nurses' Health Study, included in this analysis, previously reported a strong association with BMI at 18 years of age,⁷ but we are not aware of studies investigating the association with later premenopausal ages.

Obesity has many adverse effects on general health,³⁰ and we do not advocate weight gain as a preventative measure against premenopausal breast cancer. However, understanding the mechanistic action underlying the inverse association of premenopausal adiposity with breast cancer risk could potentially identify modifiable pathways. Because the association with BMI at ages 18 to 24 years is significant for ER-positive and ER-negative tumors, hormonal and nonhormonal mechanisms might be involved. Breast tissue is particularly susceptible to carcinogens between menarche and first childbirth,³¹ and the extent of this susceptibility may be influenced by childhood adiposity. Increased adiposity has a strong association with early pubertal onset but also slower pubertal tempo,³² including slower peak growth,³³ and rapid adolescent growth has been associated with increased breast can-

cer risk.³⁴ The estrogenic effects of being overweight in childhood, when adipose tissue is the major site of estrogen release, have been proposed to induce early breast differentiation or to increase the expression of tumor suppressor genes.³⁵ Being underweight during adolescence, in contrast, might result in immature differentiation due to lack of breast fat and/or low levels of ovarian hormones during breast development.³⁶

Early-adulthood adiposity is associated with intermediate markers of breast cancer risk, such as benign breast disease,³⁷ mammographic density,³⁸ and insulinlike growth factor 1 levels.³⁹ Greater mammographic density has a positive association with breast cancer risk,⁴⁰ and a more endomorphic somatotype in childhood and early adulthood is associated with lower mammographic density throughout adulthood.³⁸ In the Nurses' Health Study,⁴¹ 82% of the association of BMI at 18 years of age with breast cancer risk was explained by mammographic density, and breast density may be an intermediate factor in the biological pathway for breast cancer development. However, the mechanism of how density affects risk is not well understood, and the amount of nondense (ie, fatty) tissue, with which BMI is strongly correlated, is also inversely associated with breast cancer risk, independently of percentage density.⁴⁰ Early-life body size might also affect long-term insulinlike growth factor 1 levels implicated in breast cancer risk,⁴² given that plasma insulinlike growth factor 1 levels at ages 32 to 70 years were reported to be 14% lower in women who were overweight compared with those who were lean at age 18 years.³⁹

The inverse association of BMI in premenopausal women 25 years or older with predominantly hormone receptor-positive rather than hormone receptor-negative breast cancer implies a hormonal mechanism. Estrogen synthesis, through the aromatase enzyme in subcutaneous fat, represents about 5% of total estradiol synthesis in premenopausal women, but with extreme obesity, negative feedback in the hypothalamic-pituitary-axis can lead to switch off of normal ovarian function and be reflected in amenorrhea.⁴³ Irregular menstrual or fewer ovulatory cycles have therefore been suggested as possible explanations for the inverse association,⁴⁴ but this suggestion has not been supported by studies that could adjust for menstrual cycle pattern.⁹⁻¹¹ However, BMI-related differences in sex-hormone profile may contribute to the inverse association of BMI and breast cancer risk. A study⁴⁵ reported that premenopausal women with higher BMI had lower estradiol, total testosterone, sex hormone-binding globulin, and progesterone levels but greater free testosterone levels than premenopausal women with lower BMI. Positive associations of premenopausal breast cancer risk have been reported with estradiol⁴⁶⁻⁴⁹ and testosterone levels,^{46-48,50,51} possibly stronger for ER-positive and/or PR-positive breast cancer,⁴⁷ but studies have been inconsistent. Studies investigating endogenous progesterone levels,^{46,47,49-51} however, have

not found associations with breast cancer risk. Circulating levels of leptin, a peptide hormone produced primarily by adipocytes that is overexpressed in breast cancer, were also associated with reduced premenopausal breast cancer risk in a prospective study, although not independently from BMI.⁵²

Strengths and Limitations

The strengths of this collaboration are its large number of cases, providing precise estimates of relative risk by age at adiposity and allowing for stratified and breast cancer subtype-specific analyses. All contributing studies were prospective, and most had multiple follow-up rounds, facilitating determination of menopausal status and time-updated covariate information.

However, the use of BMI has its limitations in that women with the same BMI can have different body fat distributions and overall body fat levels.⁵³ Body mass index was recalled for early adulthood, but a good correlation ($r = 0.87$) has been reported between recalled and measured weight at 18 years of age.⁵⁴ Current weight was usually self-reported, but in the Sister Study,⁵⁵ 66% of women accurately reported their current weight within 1.35 kg, and underweight women tended to over-report and obese women tended to underreport, although rarely by more than 10%. If such misclassification applied to all studies, we might have slightly overestimated the trends but not to a sufficient degree to account for them fully. On the other hand, random misclassification would have led to attenuated effect sizes. Study-specific differences in method of assessment and cut points for hormone receptor and *ERBB2/HER2* status of breast cancer, given that these data were frequently obtained from medical records, may have led to differential classification of the tumor types between studies, potentially leading to underestimation of relative risks. More than 1000 breast cancer cases occurred in black women, allowing for stable estimation of relative risks in that population; results were similar to results from white women. However, we had insufficient statistical power to address the hypothesis that associations might be weaker or absent in Asian populations.^{12,13,16,56}

Conclusions

The results of our study suggest that increased BMI is inversely associated with the risk of breast cancer diagnosis before menopause, to a greater magnitude than suggested in previous analyses, and with the strongest associations for BMI at young ages. The association with BMI in early adulthood is universal across strata of other risk factors and across breast cancer subtypes. Understanding the biological mechanism underlying this association could have important implications for breast cancer prevention.

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